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13. ABSTRACT ***(Maximum 200 Words)***

This training award supports studies to describe associations between breast cancer risk and elements of energy balance. As part of an ongoing, population-based case-control study of breast cancer, associations between intentional weight loss at multiple time periods and risk of breast cancer were examined. Breast cancer patients were identified from statewide tumor registries in Massachusetts, New Hampshire, and Wisconsin from 1996-1998. Similarly aged control women were randomly selected from population lists. Information on intentional weight loss and breast cancer risk factors was obtained through telephone interviews. Data were collected for 2156 cases and 2833 controls. Logistic regression was used to compute odds ratios (OR) and 95% confidence intervals (CI). After adjustment for age, body size, number of weight loss episodes and other risk factors, reduced odds of breast cancer were observed for intentional weight loss during the teens (≥60 pounds OR=0.43, CI=0.19-0.99) and forties (40-69 pounds OR=0.60, CI=0.36-1.00). Cumulative intentional weight loss (≥120 pounds) was associated with a 43% reduction in risk (OR=0.57, CI=0.37-0.89). Associations with cumulative weight loss were more pronounced in women who gained substantial amounts of weight. These results suggest that large amounts of intentional weight loss, independent of attained weight, may be associated with a reduced risk of breast cancer.

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Suzanne M. Shaffer 10/28/99

PI - Signature Date

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INTRODUCTION

This postdoctoral training award supports studies to describe associations between elements of energy balance (physical activity, body size, intentional weight loss) and risk of breast cancer.

TECHNICAL OBJECTIVE 1 (PHYSICAL ACTIVITY)

Previously reported results from our population-based case-control study show that daily physical activity at 14-22 years of age is associated with a 50% reduction in breast cancer risk [1]. We completed analyses of effect modification by body size and weight change on the relation between early-life physical activity and breast cancer risk. The manuscript is currently under review for publication in *Cancer Epidemiology, Biomarkers and Prevention.* Appendix C contains a copy of this report.

Results from this population-based case-control study indicate that the reduced risk of postmenopausal breast cancer associated with daily physical activity at 14-22 years of age may be greatest in women who were heaviest during the same time period or who, over the adult years, either lost weight or gained only modest amounts. Compared to women with no activity and little weight gain, frequent physical activity was associated with reduced breast cancer risk in women who had lost weight since age 18 (odds ratio=0.19, 95% confidence interval=0.05-0.70), who gained little weight (0-7.3 kg, odds ratio=0.36, 95% confidence interval=0.15-0.85) or who gained modest amounts of weight (7.4-15.0 kg, odds ratio=0.31, 95% confidence interval=
0.11-0.66).

These findings suggest that daily physical activity during young adulthood may have the greatest benefit for reducing postmenopausal breast cancer risk among women who avoid substantive weight gain during adult life. In contrast, a protective effect of early-life physical activity may not exist in postmenopausal women who experience appreciable weight gain. Given the disturbing trends of an increasing prevalence of overweight/obese adults [2] and children [3, 4] in the United States, and of increasing prevalence of physical inactivity among girls [5], these findings may be relevant for future breast cancer prevention efforts.

TECHNICAL OBJECTIVE 2 (INTENTIONAL WEIGHT LOSS)

Data collection for the evaluation of intentional weight loss in relation to breast cancer risk has been completed. Preliminary analyses have been conducted and a manuscript is in preparation. Below is a summary of our findings.

Study participants and design

All female residents of Wisconsin, Massachusetts (excluding metropolitan Boston), and New Hampshire, who had a new diagnosis of invasive breast cancer and were less than 70 years of age, were eligible for this study. Case women were identified by each state's cancer registry from July 1996 through July 1998. Permission was obtained from each physician of record to interview eligible patients. Eligibility was limited to women with listed telephone numbers, drivers' licenses verified by self-report (if less than 65 years of age), and known dates of diagnosis. This on-going study has enrolled 2,156 cases, which represents approximately 80% of the eligible cancer patients.

Control subjects were selected from the community using two sampling frames: women under 65 years of age were selected from a list of licensed drivers, and women aged 65-69 years of age were selected from a roster of Medicare beneficiaries compiled by the Health Care Financing Administration. Updated computer files of potential controls were obtained annually. Controls were selected at random withing age strata to yield an age distribution similar to that of the cases within each state. Controls had no personal history of breast cancer, a listed telephone number, and, if less than 65 years of age, a driver's license (by self-report). This study has enrolled 2,833 controls which represents approximately 80% of eligible control subjects.

Data collection

Letters were sent to eligible study participants briefly describing the study before contacting them by telephone. The 45 minute telephone interview elicited information on lifetime physical activity, lifetime occupations, reproductive history, personal and family medical history, and demographic factors. Intentional weight loss was assessed with the following questions:

- Did you ever lose at least 10 pounds on purpose?
- If yes, Did you lose at least 10 pounds or more on purpose during [your teens, your twenties...during each decade of life and for the year prior to the reference age]?
- If yes, How many times did you lose 10 pounds or more?
- How much did you lose, on purpose, the [first, second, third, fourth] time?

Information on weight at each decade, weight one year prior to the reference age ('recent' weight), height at age 25, and height one year prior to the reference age was also obtained.

Statistical analysis

Intentional weight loss was expressed in several ways: as a dichotomous variable (yes/no) at each age period, as the number of episodes of weight loss at each age period, as the cumulative number of episodes of intentional weight loss, as the total amount of weight loss at each age period, and as the cumulative amount of weight loss over all age periods.

The reference age for cases was defined as their age at diagnosis. A comparable reference age for controls was defined as the median date of diagnosis for similarly-aged cases (within 5-year age strata) interviewed during the same month. Recent body mass index (BMI) (recent weight (kg) / tallest height (m^2)) was calculated and categorized into quintiles based on the distribution of control subjects. BMI at age 18 was calculated using weight at age 18 and tallest height (weight-age 18 (kg) / tallest height (m^2)). Weight change (difference between weight at age 18 and recent weight) was separated into one category of weight loss and tertiles of weight gain, with cut-points defined by the control distribution.

Odds ratios (OR) and 95 percent confidence intervals (CI) were obtained from unconditional logistic regression models [6]. All models were adjusted for age (7 levels), state (3 levels), parity (4 levels), menopausal status, family history of breast cancer, and recent BMI (5 levels). Models evaluating cumulative number of weight loss episodes included weight change (4 levels) and BMI at age 18. Stratified analyses according to weight change included BMI at age 18 as a covariate. Women with missing values for covariates were assigned to separate categories and retained in all analyses.

Reliability sub-study

To assess the reliability of the intentional weight loss questions, we re-interviewed a sequential sample of cases and controls initially interviewed in Wisconsin during October 1998. After an average of 9.5 months (range 8 -11 months), 118 cases (out of 126 possible, 94%) and 82 controls (out of 90 possible, 91%) were successfully re-contacted and re-interviewed. Kappas and 95 percent lower confidence limits (LCL) were estimated to evaluate the reproducibility of the intentional weight loss items [7]. Among women interviewed a second time, reproducibility of the interview was high (Table 1, Appendix D). The kappa for ever reporting intentional weight loss of at least ten pounds was 0.70 (LCL 0.56) for cases and 0.73 (LCL 0.57) for controls. The kappas for recall of intentional weight loss appeared greatest for intentional weight loss occurring during the teenage years (cases 0.80, LCL 0.64; controls 0.68, LCL 0.45), with moderate kappa values for the subsequent decades including the previous one (cases 0.56, LCL 0.41; controls 0.62, LCL 0.45).

Results

Women who reported ever losing at least 10 pounds on purpose tended to be younger, heavier and had greater amounts of weight gain than women who reported no intentional weight loss (Table 1, Appendix E). The association between intentional weight loss and breast cancer risk was null (Table 2, Appendix E). However, a 22% reduction in breast cancer risk was observed for those women intentionally losing weight in their teens, compared to women who never intentionally lost weight (OR=0.78, CI=0.64-0.96). For all other time periods, including the year prior to the reference date, null associations between intentionally losing weight and breast cancer risk were observed.

Associations between breast cancer risk and the number of times weight was lost is shown in Table 3 (Appendix E). Among subjects reporting ever intentionally losing at least 10 pounds, a reduced odds of breast cancer was observed for women reporting one (OR=0.78, CI=0.61-0.98) and two (OR=0.65, CI=0.42-0.99) weight loss episodes during their teens. Losing weight three times during this time period was not associated with risk. An increased risk of breast cancer was observed among women reporting losing weight only one time during their thirties (OR=1.29, CI=1.08-1.55); no associations were observed with a greater number of weight loss episodes. Estimates for the number of episodes of intentional weight loss were close to the null for all other age periods. For the cumulative number of weight loss episodes, elevated odds were observed for four and five episodes of intentional weight loss (OR=1.32, CI=0.98-1.78 and OR=1.21, CI=0.83-1.76, respectively).

Amount of intentional weight loss and risk of breast cancer in women who ever lost at least 10 pounds on purpose is shown in Table 4 (Appendix E). During the teens, lower odds of breast cancer were observed for each category of weight loss, compared to not losing weight intentionally at this age (10-29 pounds OR=0.57, CI=0.38-0.85; 30-59 pounds OR=0.35, CI=0.19-0.67; ≥60 pounds OR=0.43, CI=0.19-0.99). An inverse association between greater levels of weight loss during the thirties and breast cancer risk was observed (p-trend = 0.03). Low amounts of weight loss (10-19 pounds) was associated with an increased risk of breast cancer at this age period (OR=1.43, CI=1.08-1.89). An inverse association between weight loss and breast cancer risk was also observed for weight loss during the forties (40-69 pounds OR=0.60, CI=0.36-1.00, p-trend = 0.07). Weight loss during the twenties, fifties and sixties was not significantly associated with breast cancer risk. However, cumulative weight loss was inversely associated with risk of breast cancer; the highest amount of cumulative weight loss (≥120 pounds) was associated with a 43% reduction in risk (OR=0.57, CI=0.37-0.89, p-trend=0.01).

Cumulative intentional weight loss and breast cancer risk were stratified by weight change (Table 5, Appendix E). Cumulative amounts of intentional weight loss were inversely associated with breast cancer risk in women in the third tertile of weight gain (weight gain > 17.7 kg, p-trend=0.04). In this group, cumulative weight loss of at least 120 pounds was associated with a 49% reduction in risk, independent of the cumulative number of times weight was lost (OR=0.51, 95% CI=0.27-0.98).

Discussion

In this large study, both the number of intentional weight loss episodes and the amount of weight lost during the teen years, was associated with a reduction in breast cancer risk. A higher number of cumulative weight loss episodes appeared to be associated with an increased risk of breast cancer. However, increasing amounts of weight loss during the thirties, forties and cumulatively was associated with reductions in risk independent of the number of weight loss episodes and attained body size. Increasing amounts of cumulative weight loss appeared to be most beneficial in women who gained substantial amounts of weight.

Previous studies have shown that weight loss is inversely associated with risk of breast cancer [8, 9]. However, we are not aware of any studies that have directly addressed whether intentional weight loss (not disease-related weight loss) was associated with breast cancer risk. In one study, a reduction in breast cancer mortality associated with intentional weight loss was observed in women with obesity-related disorders [10]. However, this finding is not generalizable to breast cancer incidence. Distinguishing between intentional and disease-related weight loss, as well as identifying other patterns associated with intentional weight loss such as weight cycling, may further clarify the association between risk of breast cancer and intentional weight loss.

Few studies have examined the risk of breast cancer associated with weight cycling. Trentham-Dietz et al. [11] showed that weight cycling (weight loss of at least 20 pounds with regain of half the amount lost) was not associated with postmenopausal breast cancer risk independent of attained body size and weight gain. These results are in general agreement with our observation that frequent episodes of intentional weight loss of at least ten pounds was not associated with breast cancer risk at later age periods. It has been hypothesized that multiple episodes of weight loss with regain may be detrimental to health through pathophysiologic alterations in macronutrient metabolism, body composition or preference for high fat foods. However, weight cycling does not appear to be associated with elevated levels of fasting blood glucose or insulin, dyslipidemias, or other measures of fat metabolism [12-15]. Associations with female endogenous hormones are unclear.

Data presented here suggest that in women who are not successful at maintaining intentional weight loss but experience substantial amounts of weight gain, large amounts of intentional weight loss may associated with a reduced of odds of breast cancer. This is an important observation given the strong and consistent evidence that weight gain increases the risk of developing breast cancer [8, 16, 17]. Because weight gain may increase exposure to endogenous estrogen [20-22], multiple episodes of weight loss may interrupt this exposure by decreasing circulating estrogen levels or preventing increases.

Limitations of our study should be considered when the interpreting the results. High response rates of cases and controls make substantial selection bias unlikely. However, recall bias may be present due to our study's dependence on self-reports of intentional weight loss. Although recall bias may be a

potential limitation, the reports themselves are likely reliable. As discussed above, reproducibility of the interview was high.

Intentional weight loss is a common behavior among American women, particularly those that are overweight or obese [23] and encompasses a complex set of weight change patterns. These results suggest that repeated episodes of intentional weight loss may be detrimental with regard to breast cancer prevention, whereas large amounts of weight loss, particularly in women who had substantial weight gain, may be beneficial. The underlying biological mechanisms of these findings are not clear. Examining these associations in the context of how weight loss was achieved may help to clarify these results (see Technical Objective 3). Additionally, further analysis in sub-groups of women defined by such factors as attained body size, menopausal status and hormone replacement therapy use, may by informative.

TECHNICAL OBJECTIVE 3 (WEIGHT LOSS METHODS)

We plan to examine associations between method of weight loss and risk of breast cancer. To assess weight loss method for each episode of intentional weight loss, the following questions were included in the study interview:

- [for each weight loss episode]: And what methods did you use [up to two, from list]
- [list of weight loss methods: low calorie diet, low fat diet, skipped meals, over-the-counter diet pills, commercial weight loss program, prescription medication, exercise, laxatives or water pills, gastric surgery, regurgitation]

Data collection has recently been completed for the same 2156 breast cancer cases and 2833 population controls as described above. Analysis is in the preparation stage.

OTHER ACTIVITIES

As a complement to the above analyses we also examined the association between physical activity and endometrial cancer risk. Endometrial cancer is a hormone-mediated tumor with recent exogenous and endogenous risk factors including use of hormone replacement therapy, smoking and obesity [24-29]. We hypothesized that if the effect of physical activity was via hormone suppression, endometrial cancer incidence would also be reduced in women. Our results support this hypothesis. We found that recent moderate and vigorous physical activity were associated with a 22% and 29% reduction in endometrial cancer risk, respectively.

REFERENCES

(see Appendix F)

APPENDICES

Appendix A: List of key research accomplishments.

- Submission of paper titled "Early Life Physical Activity and Postmenopausal Breast Cancer: Effect of Body Size and Weight Change" to *Cancer Epidemiology, Biomarkers and Prevention.*
- Submission of paper titled "Recreational Physical Activity and Risk of Endometrial Cancer" to the *American Journal of Epidemiology.*
- Completion of reliability sub-study of intentional weight loss questions.
- Preliminary analyses completed on intentional weight loss and risk of breast cancer.

Appendix B: List of reportable outcomes.

- Draft manuscript: "Early Life Physical Activity and Postmenopausal Breast Cancer: Effect of Body Size and Weight Change".
- Tables describing relations between intentional weight loss and breast cancer risk.
- Table showing results from reliability sub-study of intentional weight loss.

Appendix C: Copy of "Early Life Physical Activity and Postmenopausal Breast Cancer: Effect of Body Size and Weight Change".

Early Life Physical Activity and Postmenopausal Breast Cancer:

Effect of Body Size and Weight Change

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Running Title: Physical activity and breast cancer

ABSTRACT

It is not yet known whether early-life physical activity reduces the risk of developing breast cancer. Sub-group analyses according to body size may provide a clearer understanding of this association. Data from a population-based case-control study of female residents of Wisconsin, Massachusetts, Maine and New Hampshire were used to examine associations between breast cancer risk and physical activity when 14 to 22 years of age, according to body mass index (BMI) at age 18 and weight change between age 18 and five years prior to diagnosis. Cases (n, postmenopausal=4614) were identified by each state's tumor registry; controls (n, postmenopausal=5817) were randomly selected from population lists. Frequency of participation in strenuous physical activity, weight, height and other factors were ascertained through telephone interviews. Odds ratios (OR) and 95% confidence intervals (CI) were computed using logistic regression conditioned on age and state. Models were adjusted for parity, age at first birth, age at menarche, family history, education, and age at menopause. Reductions in risk were greatest in the fourth quartile of BMI at age 18; the OR for women with the highest activity frequency was 0.45 (CI=0.26-0.79). Associations with frequency of activity also varied by weight change. Compared to women with no activity and little weight gain, frequent physical activity was associated with reduced breast cancer risk in women who had lost weight since age 18 (OR=0.19, CI=0.05-0.70) or who gained little or modest amounts of weight (weight gain: first tertile OR=0.36, CI=0.15-0.85; second tertile OR=0.31, CI=0.11-0.66). These results suggest that the reduced risk of postmenopausal breast cancer associated with daily, early-life physical activity may be greatest in women who were heaviest at age 18 or who, over the adult years, either lost weight or gained only modest amounts.

INTRODUCTION

Data are equivocal regarding the benefit of early-life physical activity in postmenopausal breast cancer prevention (1-6). In a prospective study of Norwegian women, Thune et al. (7) observed that the reduced risk of breast cancer associated with higher levels of recreational physical activity during midlife was greatest in lean women. This finding suggests that analyses in sub-groups defined by measures of body composition may provide a clearer understanding of the potential importance of physical activity in the prevention of breast cancer. High levels of energy expenditure have been correlated with a lower percentage of adipose tissue (8-12), the primary source of endogenous estrogen after menopause (13). Thus, simultaneous examination of weight, physical activity and breast cancer risk may be informative.

The purpose of this report is to expand on our previous observation of a reduced risk of breast cancer associated with regular, moderate to strenuous activity in early life (1) by evaluating whether reductions in risk were limited to certain sub-groups of postmenopausal women based on their body size at age 18 and net weight change over adulthood.

METHODS

Study participants and design

Detailed descriptions of this case-control study have been reported (14, 15). Briefly, all female residents of Wisconsin, Massachusetts (excluding metropolitan Boston), Maine and New Hampshire, who had a new diagnosis of invasive breast cancer and were less than 75 years of age, were eligible for this study. Case women were identified by each state's cancer registry from April 1988 through December 1991, except for New Hampshire, where women were enrolled beginning in January 1990. Permission was obtained from each physician of record to interview eligible patients. Eligibility was

limited to women with listed telephone numbers, drivers' licenses verified by self-report (if less than 65 years of age), and known dates of diagnosis. Of the 8,532 eligible cases, physicians refused contact for 709 cases (8.3 percent); 464 cases (5.4%) were deceased, 69 (0.8%) could not be located, and 402 (4.7%) refused to participate. The overall response rate for cases was 80.7 percent.

Control subjects were selected from the community using two sampling frames: women under 65 years of age were selected from a list of licensed drivers, and women aged 65-74 years of age were selected from a roster of Medicare beneficiaries compiled by the Health Care Financing Administration. The controls were selected to have an age distribution similar to that of the cases, but with over-sampling of younger control women in the New England states to increase the statistical power of the study. Controls had no personal history of breast cancer, a listed telephone number, and, if less than 65 years of age, a driver's license (by self-report). Of the 11,329 eligible controls, 122 (1.1%) had died, 153 (1.4%) could not be located, and 1,521 (13.4%) refused to participate, leaving 9,529 women for analysis. The overall response rate for controls was 84.2 percent.

Data collection

Letters were sent to eligible study participants briefly describing the study before contacting them by telephone. A 25 minute telephone interview elicited information on reproductive history, personal and family medical history, and demographic factors. Participation in strenuous physical activity or team sports was ascertained for two age periods: ages 14 to less than 18 years, and 18 to 22 years of age. Up to three activities and/or sports were recorded for both time periods, as was the frequency for each reported activity. Information on weight five years prior to interview ("recent weight"), and height were also obtained. For interviews after August 1988, women were also asked about their weight at age 18.

Statistical analysis

Subjects with missing or incomplete information on physical activity (256 cases, 428 controls), menopausal status (260 cases, 378 controls), and weight (recent and at age 18) or height (219 cases, 312 controls) were excluded, therefore limiting analyses to 6186 cases and 8452 controls. Analyses were further restricted to postmenopausal subjects (4614 cases, 5817 controls) because the number of premenopausal cases (n=1572) was too small for the examination of interactions with high levels of activity. Because of these exclusions, the sample size for these analyses differs from those in the original report (1). Women were classified as postmenopausal if they reported natural menopause or bilateral oophorectomy before their reference date. Women who reported hysterectomy alone and at least one remaining ovary were classified as postmenopausal if their age at surgery was in the highest decile for age at natural menopause in the control group (> 54 years for smokers and > 55 years for nonsmokers). Women's menopausal status was considered unknown if they had undergone hysterectomy without bilateral oophorectomy at an intermediate age (second to ninth decile).

The frequencies of reported strenuous physical activities were summed for each time period (14-18 years of age and 18-22 years) and expressed as the number of times per year subjects engaged in physical activity. Frequency was then averaged across the two time periods and categorized into five levels.

The reference age for cases was defined as their age at diagnosis. A comparable reference age for controls was defined as the age at interview minus the average time from diagnosis to interview for the case group within each state (range, 8-21 months). Quartiles of body mass index (weight (kg) / tallest height (m^2)) were calculated based on the distribution of control subjects. Four levels of weight change (difference between recent weight and weight at age 18) were defined: weight loss (weight change < 0) and tertiles of weight gain (weight change $\geq$ 0) based on the distribution of controls.

Odds ratios and 95 percent confidence intervals were obtained from conditional logistic regression models stratified according to age and state (16). To evaluate the joint effects of physical activity and weight variables, indicator variables representing the joint classification of frequency of activity and BMI at age 18, BMI five years prior to diagnosis (recent BMI) and weight change were constructed. All models were adjusted for parity, age at first birth, age at menarche, family history of breast cancer, education, and age at menopause. Additionally, weight at age 18 was included when evaluating recent BMI and BMI at age 18 was included when evaluating associations within weight change strata. Effect modification by BMI at age 18, recent BMI and weight change was evaluated by examining the difference in the log-likelihood between models with and without interaction terms expressed as the products of continuous variables. Women with missing values for covariates were assigned to unknown categories and retained in all analyses.

RESULTS

Daily strenuous physical activity at ages 14-22 years was associated with a 45% reduction in risk for postmenopausal breast cancer (OR=0.55, 95% CI = 0.39-0.78) (Table 1). A weak inverse trend between BMI at age 18 and postmenopausal breast cancer risk was observed (P-trend=0.05) whereas a strong, positive association was observed with recent BMI (P-trend<0.001). Weight change between 18 years of age and 5 years prior to diagnosis was positively associated with breast cancer risk (P-trend<0.001), with an OR of 1.40 (95% CI = 1.26-1.56) for the highest tertile of weight gain compared to the lowest tertile.

The relation between physical activity and risk of postmenopausal breast cancer varied according to BMI at age 18 (Figure 1, P-interaction = 0.02). Reductions in risk were most consistently observed in women who were heavier. Compared to subjects in the first quartile of BMI at age 18 who

reported no activity, the OR for women in the fourth quartile of BMI at age 18 who exercised greater than 364 times per year was 0.45 (95% CI=0.26-0.79).

Associations between physical activity and postmenopausal breast cancer risk also varied by weight change since age 18 (Figure 2, P-interaction=0.03). Among those who lost weight, the OR for the highest level of activity was 0.19 (95% CI=0.05-0.70), compared to no activity in the first tertile of weight gain. In the first tertile of weight gain, a 27% lower risk of postmenopausal breast cancer was associated with activity frequencies of 48-103 times/year (OR=0.73, 95% CI=0.54-0.98) and 104-363 times/year (OR=0.74, 95% CI=0.56-0.97), and daily activity (> 363 times/year) was associated with a 64% lower risk (OR=0.36, 95% CI = 0.15-0.85) compared to no activity. Within this stratum, the inverse relation was statistically significant (P-trend=0.001). In the second tertile of weight gain, a lower odds of breast cancer was observed only with the highest frequency of activity (OR = 0.31, 95% CI = 0.11-0.66), compared to no activity in the first tertile of weight gain. Physical activity was not associated with breast cancer risk in the highest tertile of weight gain.

Effect modification of BMI-recent on the relation between frequency of physical activity and postmenopausal breast cancer was not evident (P-interaction=0.48). Additionally, in all models, results were less strong when examining physical activity/breast cancer associations using energy expenditure scores (MET scores) (17) assigned to the specifically reported physical activities (data not presented).

DISCUSSION

Results from this study suggest that the reduced risk of postmenopausal breast cancer associated with daily physical activity at 14-22 years of age may be greatest in women who were heaviest within the same time period or who, over the adult years, either lost weight or gained only

modest amounts. Among women who were heaviest at age 18, risk of postmenopausal breast cancer was reduced by about 50% in those who exercised frequently.

More pronounced were results obtained from the model examining the joint effects of early-life physical activity and net lifetime weight change. Risk of postmenopausal breast cancer was reduced by about 80% among women who were active on a daily basis as young adults, and who lost weight between age 18 and 5 years prior to diagnosis, independent of initial weight. However, given the small sample size of this subgroup, the stability of this estimate is questionable. Interestingly, among women with little lifetime weight gain (first tertile), reduced risk of breast cancer was observed at lower levels of early-life activity, a pattern not observed in any other weight change subgroup. In higher strata of weight gain, the inverse association between physical activity and cancer risk diminished such that the reduced risk of breast cancer associated with frequent activity was not evident among women who gained the most weight.

Limitations of our study should be considered in the interpretation of results. High response rates of cases and controls make substantial selection bias unlikely. However, our study's dependence on self-reports of physical activity and body size makes it susceptible to recall bias. Information was obtained on strenuous physical activity that occurred many years before the interview. Although we cannot rule out that the subjects' reporting of past activity could reflect an association with recent activity, which was not assessed, the reports themselves are likely reliable. In a reproducibility sub-study of 203 women, the Spearman correlation coefficients between frequency of activity in the two interviews was found to be 0.60 (1). Similarly, Spearman correlation coefficients between reports of body size in two interviews indicated excellent reproducibility (weight at age 18: r=0.92; recent weight: r=0.92; height: r=0.95) (18). Other studies have reported similar levels of reproducibility (19-21).

In this study, the sample size of those with daily activity was limited. Thus, there is some uncertainty in our risk estimates at high levels of activity, which is a particular concern in light of the lack of a clear dose response. Data were not collected on physical activity during other life periods. It is possible that the group who exercised in early life and avoided weight gain is enriched with women who were relatively active throughout their lives. Thus, early life activity may reflect later life activity in this subgroup. Alternatively, weight gain may reflect inactivity after ages 14-22. Because our study lacks the relevant data, we could not adjust for the potential confounding effect of later life physical activity on breast cancer risk in these subgroups. Finally, weight change represents net change over many years; intermittent fluctuations were not assessed, nor was intentionality of weight change.

Results from two studies (1, 5) provide strong overall support of an inverse association between activity early in life and postmenopausal breast cancer (range 50%-54%), but other studies have not reported similar findings (2-4, 6). The strong and adverse effect of weight gain on postmenopausal breast cancer (18) may obscure any inverse associations between early-life physical activity and risk when evaluating an overall effect. To our knowledge, no studies have specifically evaluated how associations between physical activity during late adolescence/young adulthood and risk of postmenopausal breast cancer may differ according to early-life body size and subsequent weight change. Our results are in general agreement with a prospective study of Norwegian women (7) which included both pre- and postmenopausal women. In this study, Thune et al. (7) observed that the reduction in breast cancer risk associated with recreational physical activity assessed one year prior to baseline, was greatest in lean women (baseline BMI <22.8 kg/m^2). For most subjects in the Norwegian study, baseline assessment of physical activity and body size was at mid-life. These results are in general agreement with results from our analyses with weight change. Women who lost weight (median change = -4.5 kg) or who gained small amounts (first tertile, median weight gain = 4.5 kg)

were also the lightest five years prior to diagnosis (median recent BMI = 20.7 kg/m^2 and 21.9 kg/m^2, respectively). If the Norwegian women in the first tertile of BMI were similar, with respect to net weight change, to the women in our study who lost weight or gained little, then the reduced risk of postmenopausal breast cancer in our study is similar.

In summary, these current findings suggest that daily physical activity during young adulthood may have the greatest benefit for reducing postmenopausal breast cancer risk among women who avoid substantive weight gain during adult life. In contrast, a protective effect of early-life physical activity may not exist in postmenopausal women who experience appreciable weight gain. Given the disturbing trends of an increasing prevalence of overweight/obese adults (22) and children (23, 24) in the United States, and of increasing prevalence of physical inactivity among girls (25), these findings may be relevant for future breast cancer prevention efforts.

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Table 1. Odds ratios (OR) and 95% confidence intervals (CI) of postmenopausal breast cancer according to level of early life physical activity, body mass index (BMI) and weight change.

	cases (n=4614)	controls (n=5817)	OR (95% CI)
Frequency of activity (times per year)*			
0	2969	3600	1
1 - 47	825	1085	0.94 (0.85-1.05)
48 - 103	368	497	0.93 (0.80-1.08)
104 - 363	397	531	0.90 (0.78-1.04)
> 363	55	104	0.55 (0.39-0.78)
			P-trend = 0.002
Body mass index (quartiles)			
Age 18 (kg/m^2)†			
< 18.6	1191	1451	1
18.7 - 20.1	1173	1456	0.97 (0.97-1.09)
20.2 - 21.8	1094	1437	0.89 (0.79-1.00)
> 21.8	1156	1473	0.92 (0.82-1.03)
			P-trend = 0.05
Recent (kg/m^2)†			
< 21.8	1035	1478	1
21.9 - 23.8	1043	1435	1.06 (0.94-1.19)
23.9 - 26.5	1147	1438	1.11 (0.99-1.25)
> 26.5	1389	1466	1.33 (1.18-1.49)
			P-trend < 0.001
Weight Change (kg)‡			
< 0	326	537	0.89 (0.75-1.05)
0 - 7.3	1181	1710	1
7.4 - 15.0	1361	1777	1.12 (1.00-1.29)
> 15.0	1746	1793	1.40 (1.26-1.56)
			P-trend < 0.001

* Physical activity estimates adjusted for BMI at age 18, age at first full-term pregnancy, parity, age at menarche, family history of breast cancer, education, and age at menopause.

† BMI estimates adjusted for frequency of physical activity and other covariates listed above.

‡ Weight change estimates adjusted for frequency of physical activity, BMI at age 18 and other covariates listed above.

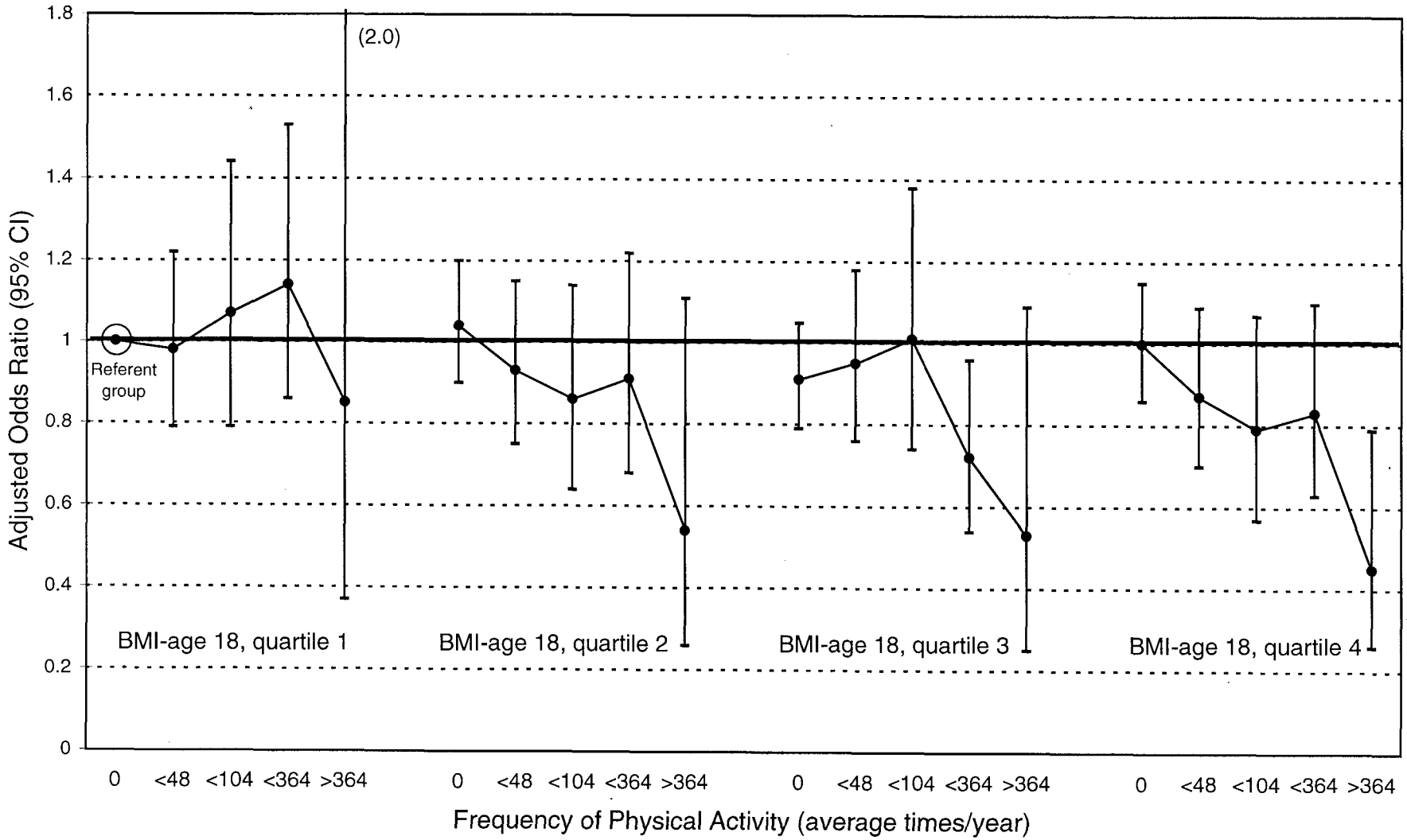

Figure 1.
Adjusted odds ratios of postmenopausal breast cancer according to body mass index at age 18 (BMI-age 18) and frequency of physical activity, 14-22 years of age.

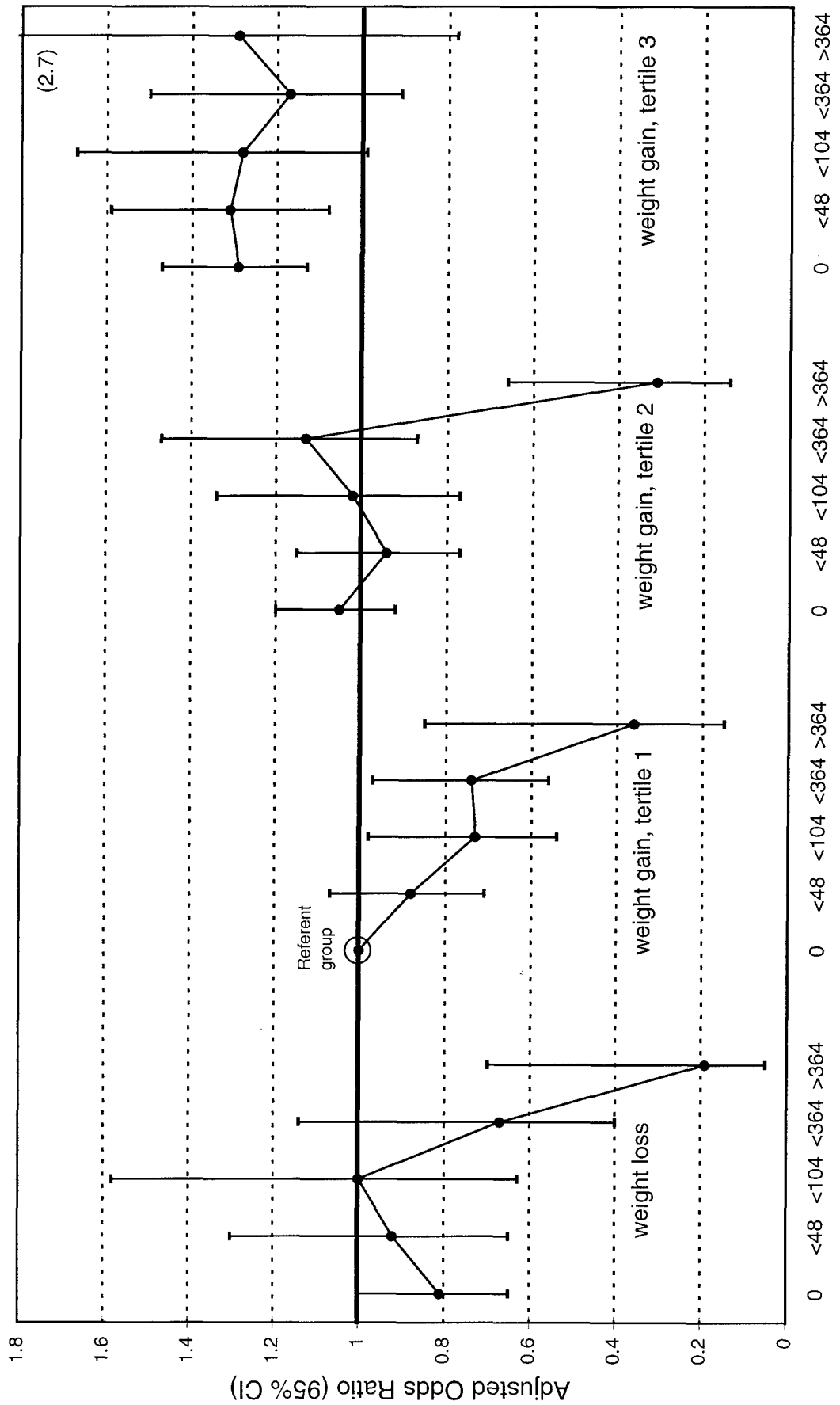

Figure 2.
Adjusted odds ratios of postmenopausal breast cancer according to weight change (age 18 to recent) and frequency of physical activity, 14-22 years of age. The multi-variable model also includes body mass index at age 18.

Appendix D: Table showing results from reliability sub-study of intentional weight loss.

Table 1. Kappas (and 95% lower confidence limits) of the intentional weight loss questions among breast cancer cases and population controls, Wisconsin 1998-1999

Intentional weight loss of at least 10 pounds (Yes vs No)	Cases N=118	Controls N=82
Ever	0.70 (0.56)	0.73 (0.57)
In teens	0.80 (0.64)	0.68 (0.45)
In 20s	0.62 (0.45)	0.49 (0.27)
In 30s	0.53 (0.37)	0.50 (0.29)
In 40s	0.50 (0.31)	0.48 (0.27)
In 50s	0.73 (0.57)	0.51 (0.28)
In 60s*	0.29 (0)	0.72 (0.35)
In the previous decade	0.56 (0.41)	0.62 (0.45)

*The average age of the reliability sub-study participants was 54 years (range 32-68), so that the number of cases (N=2) and controls (N=3) in the sub-study who reported intentional weight loss in their sixties was limited.

Appendix E: Tables describing relations between intentional weight loss and breast cancer risk.

TABLE 1. Selected characteristics of women with breast cancer (n=2156) and population controls (n=2833) according to intentional weight loss status.

	Intentional Weight Loss Status							
	Cases				Controls			
	Never		Ever		Never		Ever	
	N	%	N	%	N	%	N	%
Age (years)								
< 45	132	15.1	243	19.0	194	17.6	341	19.7
45 - 49	147	16.8	198	15.5	151	13.7	329	19.0
50 - 54	127	14.5	236	18.4	133	12.1	279	16.1
55 - 59	133	15.2	217	16.9	161	14.6	281	16.2
60 - 64	137	15.7	177	13.8	188	17.0	242	14.0
65 - 69	199	22.7	210	16.4	276	25.0	258	14.9
Recent body mass index (kg/m^2)								
< 22.0	313	35.8	158	12.3	410	37.2	186	10.7
22.0 - 24.0	209	23.9	206	16.1	261	23.7	273	15.8
24.1 - 26.4	147	16.8	246	19.2	197	17.9	338	19.5
26.5 - 29.5	134	15.3	289	22.6	141	12.8	433	25.0
≥ 29.6	67	7.7	372	29.0	83	7.5	480	27.8
Unknown	5	0.6	10	0.8	11	1.0	20	1.2
Weight change (kg)*								
< 0	66	7.5	89	6.9	88	8.0	115	6.6
0 - 6.4	245	28.0	186	14.5	328	29.7	262	15.1
6.5 - 13.1	235	26.9	254	19.8	294	26.7	377	21.8
13.2 - 20.9	186	21.3	316	24.7	217	19.7	433	25.0
> 20.9	129	14.7	407	31.8	157	14.2	495	28.6
Unknown	14	1.6	29	2.3	19	1.7	48	2.8

TABLE 1, continued. Selected characteristics of women with breast cancer (n=2156) and population controls (n=2833) according to intentional weight loss status.

	Intentional Weight Loss Status							
	Cases				Controls			
	Never		Ever		Never		Ever	
	N	%	N	%	N	%	N	%
Menopausal status								
Premenopausal	338	38.6	565	44.1	412	37.4	774	44.7
Postmenopausal	227	25.9	374	29.2	300	27.2	529	30.6
Unknown	310	35.4	342	26.7	391	35.4	427	24.7
Family history of breast cancer								
No	756	86.4	1104	86.2	1021	92.6	1547	89.4
Yes	103	11.8	166	13.0	66	6.0	143	8.3
Unknown	16	1.8	11	0.8	16	1.4	40	2.3
Parity								
0	251	28.7	322	25.2	262	23.8	379	21.9
1 - 2	252	28.8	403	31.5	273	24.8	523	30.3
3 - 4	180	20.6	280	21.9	257	23.3	400	23.1
≥ 5	192	21.9	274	21.4	310	28.1	427	24.7

* Weight change calculated as the difference between recent weight and weight at age 18.

TABLE 2. Odds ratios (95% CI) of breast cancer according to intentional weight loss at each age period.

Age Period of Intentional Weight Loss	Cases		Controls		Age-adjusted		Multivariable-adjusted*	
	N	%	N	%	OR†	95% CI†	OR†	95% CI†
Overall								
Never intentionally lost	875	40.6	1103	38.9	1		1	
Lost weight at least once	1281	59.4	1730	61.1	0.93	0.83-1.04	0.94	0.82-1.06
Teens								
Never intentionally lost	875	40.8	1103	39.3	1		1	
No intentional weight loss at this age	1045	48.7	1357	48.3	0.96	0.85-1.09	0.97	0.85-1.11
Lost weight at least once	224	10.5	347	12.4	0.81	0.67-0.98	0.78	0.64-0.96
Twenties								
Never intentionally lost	875	41.0	1103	39.4	1		1	
No intentional weight loss at this age	819	38.3	1102	39.4	0.93	0.82-1.05	0.94	0.82-1.08
Lost weight at least once	441	20.7	594	21.2	0.94	0.81-1.10	0.94	0.79-1.11
Thirties								
Never intentionally lost	865	40.9	1071	39.5	1		1	
No intentional weight loss at this age	702	33.2	970	35.8	0.89	0.78-1.02	0.90	0.78-1.03
Lost weight at least once	547	25.9	670	24.7	1.00	0.87-1.16	1.03	0.87-1.20
Forties								
Never intentionally lost	791	41.2	987	40.0	1		1	
No intentional weight loss at this age	609	31.8	789	31.9	0.96	0.83-1.11	0.93	0.81-1.09
Lost weight at least once	518	27.0	694	28.1	0.92	0.79-1.07	0.91	0.77-1.08

* Multivariable models include age, recent BMI (5 levels), state, parity (4 levels), menopausal status and family history of breast cancer.
† OR, odds ratio; CI, confidence interval.

TABLE 2, continued. Odds ratios (95% CI) of breast cancer according to intentional weight loss at each age period.

Age Period of Intentional Weight Loss	Cases		Controls		Age-adjusted		Multivariable-adjusted*	
	N	%	N	%	OR†	95% CI†	OR†	95% CI†
Fifties								
Never intentionally lost	557	42.8	714	43.0	1		1	
No intentional weight loss at this age	421	32.3	523	31.5	1.02	0.86-1.21	0.97	0.81-1.16
Lost weight at least once	325	24.9	424	25.5	0.97	0.81-1.17	0.92	0.75-1.12
Sixties								
Never intentionally lost	306	48.0	387	48.3	1		1	
No intentional weight loss at this age	216	33.9	267	33.3	1.02	0.81-1.29	0.93	0.72-1.19
Lost weight at least once	115	18.1	147	18.4	0.99	0.74-1.31	0.89	0.65-1.21
Recent								
Never intentionally lost	875	45.6	1103	43.6	1		1	
No intentional weight loss at this age	868	45.2	1179	46.6	0.92	0.81-1.04	0.91	0.79-1.04
Lost weight at least once	177	9.2	246	9.7	0.89	0.72-1.11	0.90	0.72-1.13

* Multivariable models include age, recent BMI (5 levels), state, parity (4 levels), menopausal status and family history of breast cancer.
† OR, odds ratio; CI, confidence interval.

TABLE 3. Odds ratios (95% CI) of breast cancer in women who ever intentionally lost weight, according to number of episodes of intentional weight loss at each age period.

Age Period of Intentional Weight Loss	Cases		Controls		Age-adjusted		Multivariable-adjusted*	
	N	%	N	%	OR†	95% CI†	OR†	95% CI†
Teens								
No intentional weight loss at this age	1045	82.3	1357	79.6	1		1	
1 time	133	10.5	216	12.7	0.80	0.64-1.02	0.78	0.61-0.98
2 times	34	2.7	66	3.9	0.69	0.45-1.05	0.65	0.42-0.99
≥ 3 times	58	4.6	65	3.8	1.19	0.83-1.72	1.13	0.77-1.64
Twenties								
No intentional weight loss at this age	819	65.0	1102	65.0	1		1	
1 time	255	20.2	336	19.8	1.06	0.88-1.29	1.03	0.85-1.26
2 times	93	7.4	130	7.7	1.01	0.76-1.34	0.99	0.74-1.33
3 times	41	3.3	57	3.4	1.01	0.67-1.53	1.00	0.65-1.52
≥ 4 times	52	4.1	71	4.2	1.03	0.71-1.50	1.01	0.69-1.48
Thirties								
No intentional weight loss at this age	702	56.2	970	59.2	1		1	
1 time	334	26.7	373	22.7	1.25	1.05-1.50	1.29	1.08-1.55
2 times	109	8.7	157	9.6	1.00	0.77-1.31	1.05	0.80-1.38
3 times	49	3.9	58	3.5	1.19	0.80-1.76	1.24	0.83-1.85
≥ 4 times	55	4.4	82	5.0	0.95	0.66-1.36	0.94	0.65-1.35
Forties								
No intentional weight loss at this age	609	54.0	789	53.2	1		1	
1 time	338	30.0	455	30.7	0.97	0.81-1.15	0.99	0.82-1.18
2 times	98	8.7	132	8.9	0.99	0.74-1.31	1.02	0.77-1.37
≥ 3 times	82	7.3	107	7.2	1.00	0.74-1.37	0.98	0.72-1.35

* Multivariable models include age, recent BMI (5 levels), state, parity (4 levels), menopausal status and family history of breast cancer.

† OR, odds ratio; CI, confidence interval.

TABLE 3, continued. Odds ratios (95% CI) of breast cancer in women who ever intentionally lost at least 10 pounds, according to number of episodes of intentional weight loss at each age period.

Age Period of Intentional Weight Loss	Cases		Controls		Age-adjusted		Multivariable-adjusted*	
	N	%	N	%	OR†	95% CI†	OR†	95% CI†
Fifties								
No intentional weight loss at this age	421	56.4	523	55.2	1		1	
1 time	231	31.0	306	32.3	0.94	0.76-1.17	0.94	0.76-1.18
2 times	54	7.2	79	8.3	0.86	0.59-1.24	0.85	0.58-1.24
≥ 3 times	40	5.4	39	4.1	1.30	0.82-2.05	1.24	0.77-1.99
Sixties								
No intentional weight loss at this age	216	65.3	267	64.5	1		1	
≥ 1 time	115	34.7	147	35.5	0.97	0.71-1.31	0.96	0.71-1.31
Recent								
No intentional weight loss at this age	868	83.1	1179	82.7	1		1	
≥ 1 time	177	16.9	246	17.3	0.98	0.79-1.21	0.99	0.80-1.23
Cumulative								
1time	533	42.2	703	41.9	1		1	
2 times	258	20.4	355	21.1	0.97	0.79-1.18	0.98	0.80-1.20
3 times	135	10.7	215	12.8	0.84	0.65-1.07	0.86	0.67-1.11
4 times	107	8.5	110	6.6	1.29	0.96-1.72	1.32	0.98-1.78
5 times	59	4.7	69	4.1	1.16	0.81-1.68	1.21	0.83-1.76
≥ 6 times	171	13.5	227	13.5	1.00	0.80-1.26	1.00	0.79-1.27

* Multivariable models include age, recent BMI (5 levels), state, parity (4 levels), menopausal status and family history of breast cancer.
† OR, odds ratio; CI, confidence interval.

TABLE 4. Odds ratios (95% CI) of breast cancer in women who ever intentionally lost at least 10 pounds according to the total amount of weight lost at each age period.

	Cases		Controls		Multivariable-adjusted*	
Weight Loss (pounds)	N	%	N	%	OR†	95% CI†
Teens						
0	1045	82.7	1357	80.0	1	
10 - 29	120	9.5	180	10.6	0.57	0.38-0.85
30 - 59	68	5.4	122	7.2	0.35	0.19-0.67
≥ 60	30	2.4	37	2.2	0.43	0.19-0.99
						p-trend=0.26‡
Twenties						
0	819	65.8	1102	65.3	1	
10 - 19	140	11.2	173	10.3	1.05	0.78-1.41
20 - 39	163	13.1	213	12.6	0.95	0.67-1.36
40 - 69	81	6.5	141	8.4	0.69	0.41-1.16
≥ 70	42	3.4	59	3.5	0.86	0.44-1.69
						p-trend=0.21‡
Thirties						
0	702	56.6	970	59.7	1	
10 - 19	174	14.0	174	10.7	1.43	1.08-1.89
20 - 39	203	16.4	253	15.6	1.23	0.90-1.68
40 - 69	118	9.5	160	9.9	1.11	0.71-1.75
≥ 70	43	3.5	67	4.1	0.94	0.53-1.68
						p-trend=0.03‡
Forties						
0	609	54.5	789	53.7	1	
10 - 19	181	16.2	241	16.4	0.92	0.68-1.24
20 - 39	202	18.1	228	15.5	1.01	0.69-1.46
40 - 69	84	7.5	147	10.0	0.60	0.36-1.00
≥ 70	41	3.7	64	4.4	0.64	0.34-1.17
						p-trend=0.07‡

TABLE 4, continued. Odds ratios (95% CI) of breast cancer in women who ever intentionally lost at least 10 pounds according to the total amount of weight lost at each age period.

Weight Loss (pounds)	Cases		Controls		Multivariable-adjusted*	
	N	%	N	%	OR†	95% CI†
Fifties						
0	421	57.0	523	55.4	1	
10 - 19	106	14.3	170	18.0	0.88	0.60-1.29
20 - 39	133	18.0	164	17.4	1.16	0.74-1.84
≥ 40	79	10.7	87	9.2	1.35	0.74-2.49
						p-trend=0.95‡
Sixties						
0	216	65.3	267	64.5	1	
10 - 29	77	23.3	104	25.1	0.95	0.67-1.35
≥ 30	38	11.5	43	10.4	1.00	0.61-1.62
						p-trend=0.96‡
Cumulative						
10 - 19	312	25.0	396	23.8	1	
20 - 29	194	15.6	279	16.8	0.86	0.68-1.10
30 - 39	164	13.2	224	13.5	0.92	0.70-1.19
40 - 49	122	9.8	147	8.8	1.01	0.74-1.38
50 - 69	160	12.8	205	12.3	0.89	0.65-1.21
70 - 89	91	7.3	123	7.4	0.82	0.56-1.21
90 - 119	88	7.1	101	6.1	0.87	0.57-1.34
≥ 120	115	9.2	189	11.4	0.57	0.37-0.89
						p-trend=0.01‡

* Multivariable models include age, recent BMI (5 levels), state, parity (4 levels), menopausal status, family history of breast cancer and number of times lost weight during the same decade.
† OR, odds ratio; CI, confidence interval.
‡ p-trend based on continuous variable.

Table 5. Odds ratios* and 95% confidence intervals (CI) of breast cancer according to cumulative weight loss in strata of weight change †.

Cumulative weight loss (pounds)	WEIGHT CHANGE (kg)							
	< 0		0 - 8.6		8.7 - 17.7		> 17.7	
	case/control	OR, CI	case/control	OR, CI	case/control	OR, CI	case/control	OR, CI
10 - 19	36 / 49	1	89 / 117	1	96 / 144	1	100 / 94	1
20 - 29			42 / 73	0.72, 0.44-1.18	70 / 97	1.07, 0.70-1.64	66 / 84	0.74, 0.48-1.15
30 - 39	18 / 20	1.20, 0.50-2.88	42 / 51	1.03, 0.60-1.77	43 / 51	1.31, 0.78-2.20	65 / 112	0.58, 0.38-0.90
40 - 49			20 / 29	0.79, 0.38-1.63	29 / 43	1.10, 0.59-2.02	59 / 55	1.07, 0.65-1.76
50 - 69	33 / 40	0.97, 0.36-2.57 P-trend=0.98‡	25 / 48	0.52, 0.26-1.05	42 / 57	1.07, 0.56-2.04	73 / 85	0.84, 0.52-1.37
70 - 119			29 / 38	0.63, 0.26-1.55	40 / 61	0.92, 0.43-1.98	100 / 102	0.95, 0.56-1.61
≥ 120			12 / 25	0.39, 0.12-1.26 P-trend=0.29‡	25 / 34	1.00, 0.37-2.68 P-trend=0.37‡	64 / 117	0.51, 0.27-0.98 P-trend=0.04‡

* Odds ratios adjusted for age, BMI at age 18 (continuous), state, parity (4 levels), menopausal status, family history of breast cancer, and cumulative number of times weight was intentionally lost.

† Weight change is difference in recent weight and weight at age 18.

‡ p-trend based on continuous variable.

Appendix F: References for body of report.

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Recd 8/16/2001

REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y) 9 August 2001

MEMORANDUM FOR Administrator, Defense Technical Information Center (DTIC-OCA), 8725 John J. Kingman Road, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports. Request the limited distribution statement for reports on the enclosed list be changed to "Approved for public release; distribution unlimited." These reports should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Judy Pawlus at DSN 343-7322 or by e-mail at judy.pawlus@det.amedd.army.mil.

FOR THE COMMANDER:

PHYLIS M. RINEHART
Deputy Chief of Staff for
Information Management

Encl